Reviews

Results of Lead Research: Prenatal Exposure and Neurological Consequences

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The history of advances in the understanding of the toxic effects of lead over the past 20 years is an outstanding example of how knowledge learned from research can impact public health. Measures that have had the greatest impact on reducing exposure to lead are reduction of lead from gasoline, elimination of lead solder from canned food, removal of lead from paint, and abatement of housing containing lead-based paint. Nevertheless, continuing factors that enhance risk to lead exposure, particularly during fetal life, are low socioeconomic status, old housing with lead-containing paint, and less than ideal nutrition, particularly low dietary intake of calcium, iron, and zinc. Prenatal exposure may result from endogenous sources such as lead in the maternal skeletal system or maternal exposures from diet and the environment. Experimental studies have shown that the developing nervous system is particularly sensitive to the toxic effects of lead and that a large number of the effects in the nervous system are due to interference of lead with biochemical functions dependent on calcium ions and impairment of neuronal connections dependent on dendritic pruning. There is need for more study to determine whether these effects are a continuum of prenatal lead exposure or whether prenatal exposure to lead produces unique effects. *Key words*: blood lead levels, fetal brain, fetal susceptibility, lead, mechanisms of central nervous system effects, neurological effects, pregnancy, prenatal exposure, risk factors. *Environ Health Perspect* 104:1050–1054 (1996)

Lead toxicity is one of the most studied environmental health issues and is also the most outstanding example of how knowledge learned from research can impact public health. The National Institute of Environmental Health Sciences (NIEHS) has provided support for many of the basic studies over the past 30 years, resulting in advances in understanding cellular effects of lead and effects on organ systems. Many of these accomplishments have been summarized in the NIEHS-sponsored conferences published in *Environmental Health Perspectives* (*1*) and in other published reports (*2–4*).

Research Accomplishments

The most significant research accomplishments have concerned effects of low-level exposures to lead on cognitive and behavioral development of young children. The 1992 World Health Organization/International Program for Chemical Safety Task Group on Effects of Inorganic Lead concluded that blood lead levels in young children generally below 25 µg/dl are associated with a reduction in IQ scores (*4*). The size of the apparent IQ effect as assessed at 4 years of age and above is a deficit between 1 and 5 IQ points for each 10 µg/dl increment in blood lead, with a likely size affect between 1 and 3 points. This conclusion is based on a large number of retrospective and prospective epidemiological studies and is similar to the 1991 statement from the U.S. Centers for Disease Control (*5*) and other national and international groups (*6,7*). Results of epidemiological studies to date do not provide evidence of a threshold. It is suggested that, with blood lead levels below 10 µg/dl, the effect of confounding variables and lack of precision of analytical and psychological measurements limits the ability to detect effects below the 10–15 µg/dl range. Animal studies support a causal relationship between lead and nervous system effects, and there are reports of intellectual deficits in monkeys and rats with blood lead levels in the 11–15 µg/dl range (*8*).

The result of the present awareness of lead effects has been to adopt measures that reduce human exposure to lead and reduce risks to related health effects. In 1990 and 1991, the U.S. Departments of Health and Human Services and Housing and Urban Development and the U.S. Environmental Protection Agency (EPA) published strategy documents outlining measures to reduce lead exposure (*9–11*). The measure with the probably greatest impact was the reduction of lead in gasoline, although the reasons for this action were based on broader environmental considerations. There has also been a reduction of lead in food due to reduced use of solders in food and soft drink cans. The Food and Drug Administration (FDA) Market Basket Surveys indicate that the typical daily intake of lead for a 2-year-old child dropped from 30 µg/day in 1982 to about 2 µg/day in 1991 (*12*). A federal law provides a Medicaid benefit package for all children through the Early and Periodic Screening Diagnosis and Treatment program for lead-poisoned children, including chelation therapy, vitamin and mineral supplementation, medical care, environmental investigations, education services, and nutritional and developmental assessments (*13*).

Research achievements that contribute to prevention of disease are not as dramatic as the discovery or implementation of cures for existent disease but are certainly no less important. Research regarding the health effects of lead may make a small contribution that helps millions of people, but is probably unknown to them. While these beneficial effects may not be apparent to the individuals who are spared the problems of toxicity, the implementation of measures to reduce exposure to lead are clearly visible when examined on a population basis.

Figure 1 compares blood lead levels in children 1–5 years of age in the United States as measured by the National Health and Nutrition Examination Survey (NHANES) II in 1976–1980 (Fig. 1A) to blood lead levels as measured in children by NHANES III, 1988–1991 (Fig. 1B) (*14*). In this 10-year period, the mean blood lead for persons in

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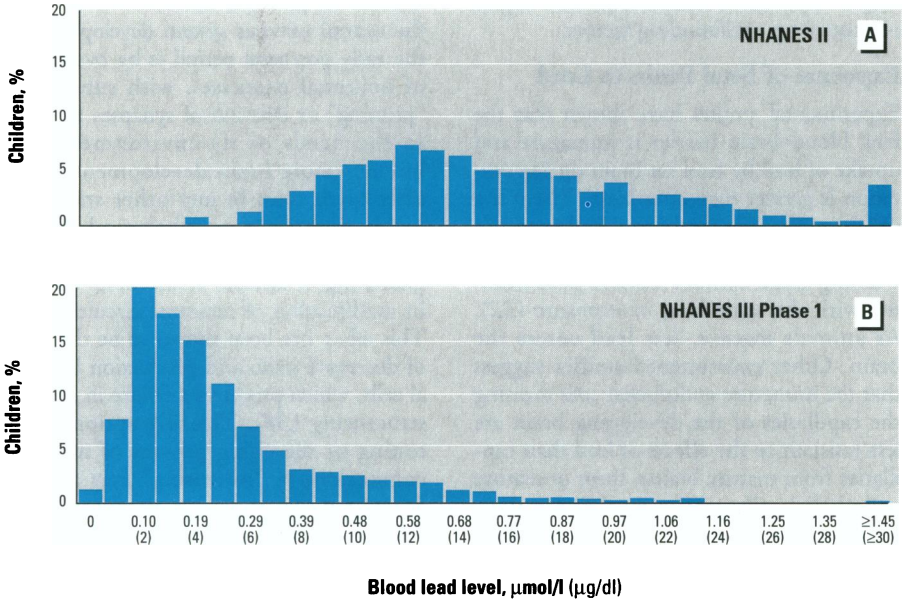

Figure 1. Blood lead levels in children 1–5 years of age in the United States as measured by NHANES II in 1976–1980 (A) versus blood lead levels as measured in children by NHANES III, 1988–1991 (B). From Pirkle et al. (*15*).

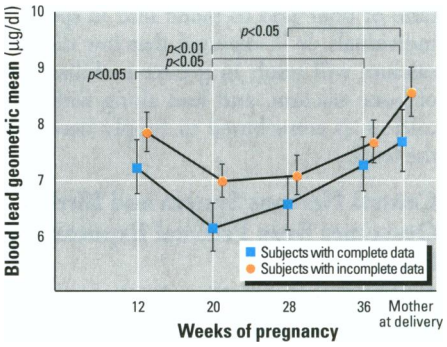

Figure 2. Plot of time course of maternal blood lead (geometric mean and SE) during pregnancy for subjects with complete and incomplete data. Incomplete data are offset on the X-axis for clarity. Upward trend of complete subjects from 20 weeks to term is significant. Ranges of horizontal lines above the data indicate significant comparisons using least significant differences post-hoc test, with indicated probabilities. Conversion factor for blood lead is 10.0 µg/dl = 0.48 µmol/l. From Rothenberg et al. (*26*).

the general population of all ages decreased by 78%, from 12.8 to 2.8 µg/dl between 1976 and 1991, and 77% for children ages 1–5 years, from 15 µg/dl to 3.6 µg/dl.

In spite of measures reducing lead exposure to date, large numbers of children in the United States have high exposure to lead and are at risk for impaired cognitive and behavioral development.

Continuing Risks to Lead Exposure and Toxicity

Many of the most important risk factors are low income and socioeconomic status, houses containing lead-based paint, and poor nutrition. In a 1988 report to Congress, the Agency for Toxic Substances and Disease Registry (ATSDR) determined that about 10% of the 1 million or so black children that live in inner city areas of large U.S. cities and have an income below the poverty level have blood lead levels greater than 15 µg/dl (*15*). Children who live in old houses with lead-containing paint and exposure to lead-containing dust are at increased risk for lead exposure and elevated blood lead levels. Lead was banned from indoor paint in the United States in 1978, so every house built before that time is likely to contain lead-based paint. This includes more than 50 million dwellings (*3*). It is estimated that at least 6 million children live in houses built prior to 1940—houses that constitute the greatest risk.

Less-than-ideal nutrition contributes to adverse consequences of lead exposure, particularly diets that are deficient in the essential minerals calcium, iron, and zinc, (*16*). Studies with experimental animals fed diets low in calcium have established that calcium deficiency increases both tissue retention and toxicity of lead (*17*). Iron deficiency also increases tissue deposition and toxicty to lead (*18*). A high prevalance of iron deficiency occurs in infants and children because of the need to expand the body's iron pool during growth; it has been observed that the children with the highest environmental exposures to lead are also at the greatest risk to iron deficiency (*19*). The most significant health impact of iron deficiency is in young children who develop defects in attention span that lead to learning deficits (*20*). A longitudinal prospective study in Yugoslavia showed that both lead exposure and iron deficiency produce effects on neurobehavior and the hemopoietic system among pregnant women, infants, and children (*21*). Lead and zinc interactions are not as well defined as those between lead and calcium and between lead and iron. Experimental studies have shown that lead increases zinc excretion (*22*) and that zinc deficiency enhances lead absorption (*23*). There is also a close inverse relationship between blood lead levels and zinc-containing heme enzymes (*24*).

Prenatal Exposures to Lead

Risk factors for prenatal exposure to lead involve maternal exposure and body burden of lead. There are both exogenous and endogenous factors contributing to maternal blood lead levels and *in utero* exposure to the fetus. Several studies have shown that there is no impairment to lead crossing the placenta and that maternal and fetal blood lead levels are similar (*25*). Today in the United States, environmental exposure to lead is largely from dietary sources for non-occupationally exposed women but, in areas of the world where leaded gasoline is still in use, airborne lead may be a significant source. Lead-glazed pottery from cottage industries may also be a potential source where such pottery is in use. Gastrointestinal absorption of lead may be increased during pregnancy along with increased calcium absorption.

The major endogenous source of lead is the skeletal system. Lead in bone reflects past exposure and may be independent of blood lead. The increase in the calcium requirement during pregnancy is accompanied by release of lead into blood which, in turn, results in fetal exposure to lead. An interesting demonstration of changes in blood lead levels during pregnancy was recently reported for 105 women living in Mexico City (*26*). The mean blood lead level for the group was 7.0 µg/dl with a range of 1.3–35.5 µg/dl, (Fig. 2). There is a significant decrease in blood lead level between 12 and 20 weeks (1.1 µg/dl). This has been explained by physiological factors such as increase in organ size and hemodilution. From week 20 to delivery, there is a linear upward trend.

Studies using stable isotope techniques have shown that about 45–75% of lead in blood is derived from bone lead in persons without excessive exposure to lead (*27,28*), and there is a further 32%–65% increase in the contribution of skeletal lead to blood lead during gestation (B.L. Gulson, personal communication). The wide variation is thought to be due to differences in the

ratio of bone lead to blood lead in specific individuals. It is expected that low dietary calcium will result in greater mobilization of bone calcium, and lead along with the calcium is contributed to supply needs of the fetus.

Central Nervous System and Birth Outcomes from Prenatal Exposure to Lead

Assessment of cognitive development in relation to prenatal exposure to lead is difficult because of limitations in assessment methodology. Nevertheless, results of prospective epidemiological studies (*29,30*) have shown that children with high umbilical cord blood lead (>10 µg/dl) have a slower sensorimotor or visual-motor development as measured by the Bayley Scales of Infant Development than children with lower blood lead levels at birth. Deficits in cognitive development with increased prenatal blood lead levels are likely to attenuate over time. Blood lead levels at 24 months of age have been found to be the most predictive of future cognitive development. Bellinger et al. (*29*) found that persistence of the cognitive deficit related to prenatal lead exposure is most often detected in those infants with either high postnatal exposure or less than optimal socioeconomic demographics.

Andrews et al. (*31*) reviewed 25 epidemiological studies to determine the relationship of prenatal lead exposure and birth outcomes. They concluded that prenatal lead exposure is unlikely to increase the risk of premature rupture of membranes but does appear to increase the risk of preterm delivery. It is unclear whether prenatal lead exposure decreases gestational age. Prenatal lead exposure appears to be related to reduced birth weight, but results vary in relation to study design and degree of control for confounding factors.

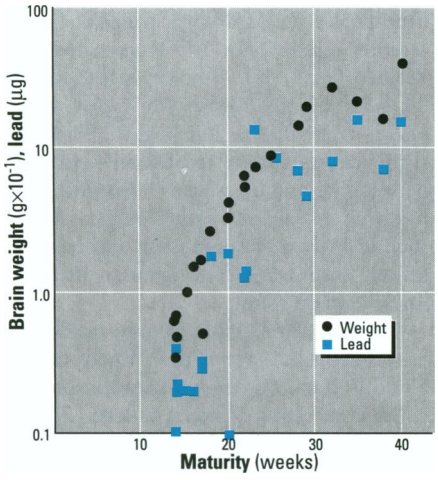

Figure 3. Relationship between brain weight and brain lead content in 21 human fetuses with maturities of 14–40 weeks. From Barltrop (*34*).

Exposure of Fetal Brain to Lead

Experimental studies have shown that the fetal blood–brain barrier is immature and uptake of lead by fetal rat brain during gestation is greater than after birth. There is a sixfold increase in total brain lead prenatally compared to a 3.5-fold increase during weaning and a twofold increase post-weaning with the same level of exposure (*32*). As animals mature, less lead enters the brain. Other experimental studies suggest that the immature endothelial cells forming the capillaries of the developing brain are less resistant to the effects of lead than capillaries from mature brains; these immature endothelial cells permit fluid and cations including lead to reach newly formed components of the brain, particularly astrocytes and neurons (*33*).

There are few studies of uptake of lead by the human brain during development. The largest number of lead measurements in fetal brain have been reported by Barltrop (*34*) in 21 human fetuses with maturities of 14–40 weeks, (Fig. 3). There was a direct relationship between brain weight and brain lead content, but there was no change in lead concentration. There was also a parallel increase in calcium; it has been suggested that movement of lead into the fetal brain, as well as other tissues, follows the movement of calcium. Studies in guinea pigs have shown that transfer of lead from mother to fetus is linearly related to umbilical cord blood flow rate (*35*).

Mechanisms for Neurological Effects of Lead

Clinical and experimental studies have provided insights regarding the mechanisms whereby lead produces neurological effects on the developing brain as studied postnatally (*36*). Mechanisms for neurological effects as studied postnatally are likely to be a continuum of prenatal effects; however, it is not known whether there are unique prenatal neurological effects.

Effects of lead on the developing brain are both morphological and pharmacological.

- Neuropharmacological
  - -Lead substitutes for calcium
  - -Neurotransmitter Release
  - -Protein kinase C
  - -Na–Ca ATPase
  - -Energy metabolism
- Neurodevelopmental (morphological)
  - -Interference with adhesion molecules
  - -Impaired programming of cell:cell connections
  - -Miswiring of central nervous system (CNS).

One of the principal mechanisms by which the central nervous system develops during the early postnatal period is by overgrowth of neuronal processes, with subsequent "pruning" or deletion of synapses to adjust to the needs of its environment. For humans more brain development occurs after birth than in any other species. A highly significant morphological effect is the result of lead impairment of timed programming of cell:cell connections resulting in modification of neuronal circuitry (*37*). This effect has been shown to be the result of decreased sialic acid production by neural cells, which produces a failure in synaptic structuring (*38*). This disruption of the toning or matching process of neuronal connections or "miswiring" may produce functional effects. It has also been found that lead induces precocious differentiation of the glia upon which cells migrate to their eventual positions during structuring of the brain, further enhancing the likelihood of alterations in normal development (*39*).

Lead functions pharmacologically by interfering with synaptic mechanisms for neurotransmitter release. It has been suggested that lead can substitute for calcium and possibly zinc in ion-dependent events at the synapse and is responsible for the observed impairment by lead of various neurotransmitter systems (cholinergic, GABergic, and dopaminergic) (*36,40*). The neonatal period has been found to be most sensitive to inhibitory action of lead on *N*-methyl-D-aspartate receptor–ion function channels (*41*). *In vitro* studies on brain capillaries have shown that micromolar concentrations of lead activate protein kinase C, a second messenger in the regulation of cellular metabolism (*42*). Lead may also replace calcium in calmodulin-dependent reactions, inhibit membrane-bound Na^+, K^+-ATPase, and interfere with mitochondrial release of calcium with impairment of energy metabolism (*43*). These effects are potentially reversible if lead can be removed from active sites. Although removal from lead exposure and chelation therapy lower blood lead levels, there is little or no information regarding effects from removal of lead from these sensitive molecular sites (*44*).

In spite of the demonstrated morphological and pharmacological effects of lead in the maturing brain, it is difficult to demonstrate a functional or clinical effect in the child under 2 years of age because of the immaturity of the brain and limited number of functions that can be tested at that age. There is no consistent lead neuropsychological syndrome or behavioral signature that can be identified clinically (*45*). In some studies, lead is most closely

related to loss in verbal skills; in others, it is nonverbal skills. Studies of cohorts of children with postnatal exposure to lead determined that the perceptual-motor subsets of the McCarthy Scales of Children's Abilities were particularly sensitive to lead exposure (*46*). Lead related losses in visual motor integration, poorer performance on tasks of serial learning, and increased errors in tasks requiring perseverance in experimatal animal models are generally consistent with clinical findings and are thought to pinpoint the hippocampus as the primary target for neurobehavioral effects (*47–50*). Also, the hippocampus is known to accumulate lead in humans (*51*) and rat pups exposed to lead (*52*). However, Lilienthal et al. (*53*) found that the behavioral profile in rats with chemically induced lesions of the hippocampus differed from patterns obtained in rats with prenatal exposure to lead and that chemical lesions of the amygdala show a greater similarity with lead-induced effects, suggesting that the hippocampus is not the sole target for lead toxicity.

Summary

Advances in the understanding of the toxic effects of lead is an outstanding example of how knowledge learned from research can impact public health. Reduction of lead in gasoline, elimination of lead solder from canned food, removal of lead from paint, and abatement of housing containing lead-based paint are important contributions to reduction of lead exposure. Factors that enhance risk to lead exposure, particularly during fetal life, are low socioeconomic status, old housing with lead-containing paint, and less than ideal nutrition, particularly low dietary intake of calcium, iron, and zinc. Prenatal exposure may result from endogenous sources such as lead in the maternal skeletal system or maternal exposures from diet and the environment.

The developing nervous system is particularly sensitive to the toxic effects of lead, and experimental studies have shown that a large number of the effects in the nervous system are due to interference by lead with biochemical functions dependent on calcium ions and impairment of neuronal connections dependent on dendritic pruning.

In spite of past efforts, there are many important avenues for further research, particularly with regard to prenatal exposures and neurological effects. Ongoing studies using stable-isotope techniques should provide new information regarding maternal–fetal transfer of lead. There is need for a better understanding of the mechanisms for the toxic effect of lead on the nervous system and also to determine whether effects from postnatal exposure are a continuum of prenatal lead exposure or whether prenatal exposure to lead produces unique effects.

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